CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA

DIVISION OF BIOLOGY
KERCKHOFF LABORATORIES OF BIOLOGY

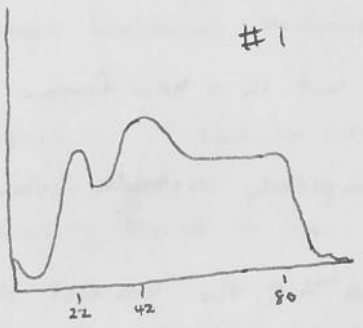
March 3, 1955

Dear Francis

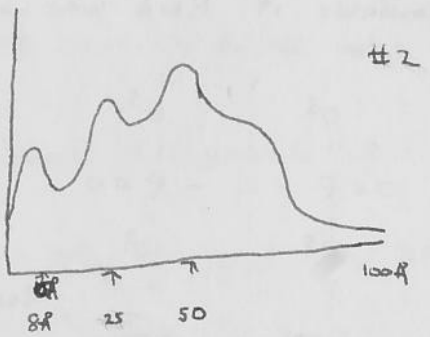
To start with, I warn you to accept this letter with marked scepticism. For there is a good chance that everything it states will turn out to be either wrong or at best trivial. They concern our favorite virus TMV.

The localization of the RNA within a central core is now a solid fact. The problem now is to determine its structure when within TMV. Naturally x-rays are the only hope so let us look at the Fourier which Don Caspar believes most probable. The sign combination is $+,-,\underset{\downarrow}{-}+-+-$. It produces a peak at 22Å which must be the phosphates. The only other Fourier which might be right derives from the $+--+-+-+$ combination and I believe is the one found by Rosy

#1



#2

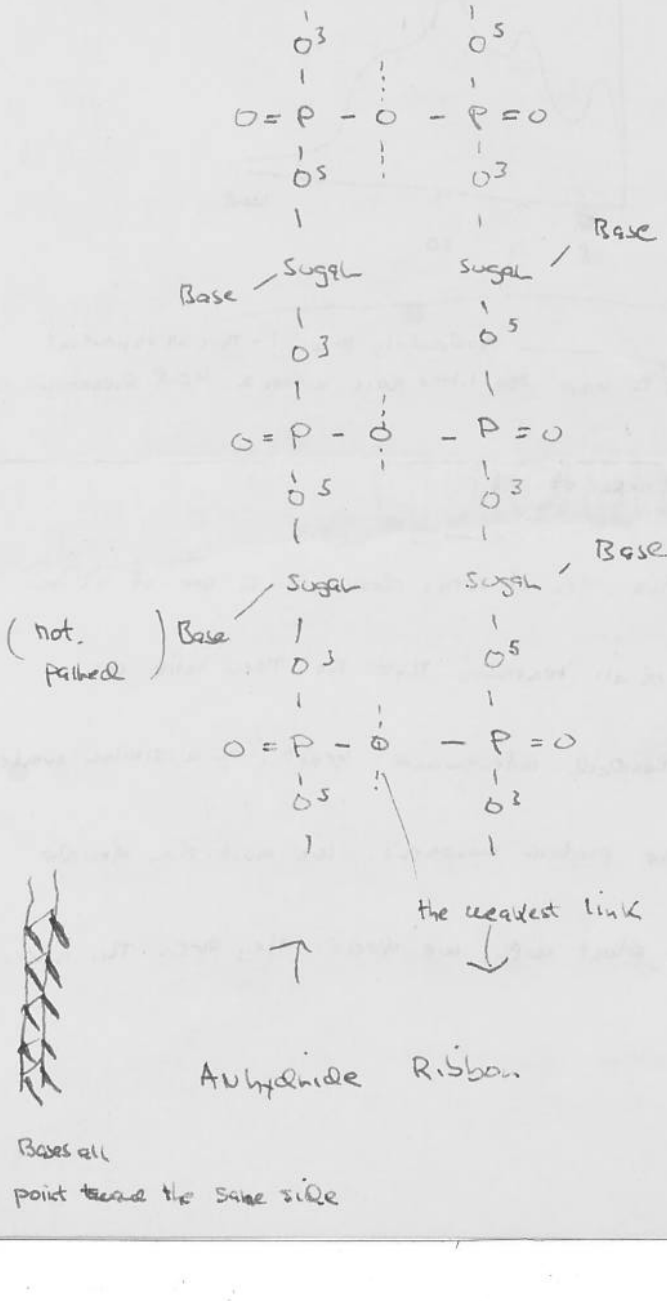


Don does not like it since it fails to converge ≈ 80Å and seems to have too little mass within a 40Å diameter core moderately phony! - this is important for the RNA. We thus base all our speculations upon the correctness of #1.

If all of the phosphates are located at a constant radius, then it seems desirable to see if it can interact in a systematic manner with the protein shell. We first of all remember that the TMV helix can alternately be considered a one stranded helix, or a 12 stranded intertwined beast (or a similar number such as 10 or 14) it just depends how we want to link up the protein monomers. We must then decide whether all of the ~~bases~~ nucleotides are equivalent. Of course to start with, we decide they are. This makes

implausible a one stranded RNA rope with 22A° pitch and turns our thoughts towards many stranded structures - say 12 or 14.

To judge its plausibility we refer to the MW of TMV RNA. It starts out as 2,500,000 (Sinsheimer) but rapidly falls to something (Cohen & Stanley JBC. 144(1942) ≃ 300,000. Recently Norman Simons has reinvestigated RNA from TMV using Xylene Sulphonate to get it out. The sedimentation constant is 13 ± 5 and the $D_{20} = 2 \times 10^{-7}$. The MW seems to be at 330,000 and may be greater as the material is definitely unstable and not too homogenous. Notice that $\frac{3.5 \times 10^6}{3.3 \times 10^5} \simeq 6.7$ - Also that this is the material which gives us our mediocre x-ray pictures, which at times I thought to be DNA like. It cannot be a simple single chain since Markham (Knight also!) finds one end group / 50 - And that its more stable (Cohen & Stanley) at pH 4 than at 7. Of course we detect branches but can't almost everything be understandable if RNA were not RNA but the following beast.



Thus the anhydride survived but in a new form. We have to postulate that its completely unstable when its protein coat is removed and that the weakest link is the P-O-P pyrophosphate bond. However rarely a P-O-C bond goes instead and Roy Markhams end groups arise.

The idea has two main merits. First it can be checked by isolating the RNA in the presence of H_2O^{18} We should find one O^{18} atom per pair of P atoms This experiment will take time but is already being planned and we may have an answer in 6-8 weeks. It will take time to get the TMV, etc.

PP/CRI/D/2/45

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Secondly the structure is surprisingly neat crystallographically. It almost seems a natural and so I believe we must consider the possibility of its existing some place even if the virus crpt gives a negative result. It can be built with DNA - of course the bases are not paired but maybe during replication it might exist. I urge you to build it and to see if your reactions compare with mine.

It naturally intrigues me for if true it would make RNA a high energy host. I would guess that RNA is not a passive template (the high turnover expts glare at us) and that the attempts of Leslie and I to thrust a simple template role were bound to failure. Right now I feel, that some serious thinking about biochemical mechanisms is in order. However I can't yet push myself to do this until the O^{18} result comes in. I have no ideas at all about the base arrangement or about its replication but I suspect something should be seen. And maybe the similarity to co-enzymes is not coincidental e.g. DPN. If any of these speculations are true, then the whole story is going to be much more complex than originally thought but still nice in that it would combine the biochemical synthesis with the molecular model approach.

The hypothesis would simply explain our bad x-ray pictures since what we are looking at is a disorganized double helix devoid of pairing. It points to the Plant Viruses as the "Secret of Life" and makes even more desirable a solution of their structure. At present I think the most fruitful thing is to obtain a Fourier from PVX. Is Rosie doing anything along these lines? Are you interested. Now is the growing time for plant viruses and it would be splendid if Roy Markham could be seduced to obtaining you large amounts. We shall try to obtain some in Berkeley and I shall

brings some with me to Cambridge in early July. However I think its risky to count on these atlantic sources. The x-ray tubes here are too weak to accomplish anything worthwhile. Sturtevant is not a man (technician!!) to be pushed.

These ideas of mine are admittedly wild. However I have a strong feeling that our correct thoughts are getting nowhere and that a radical idea will be necessary before RNA begins to make sense. I think they must come from good chemical intuition and on this score I feel particularly weak. Nevertheless we are badly in need of hypotheses (possibly even published) in order to push additional people to think along these lines. At present I have the feeling I am the only person (with possible the exception of you) who is seriously attempting to crack the bloody structure. I do not like to be this exclusive and unfortunately the coding approach only makes me feel more isolated. You complain of the isolation at Cambridge. At least there [redacted] noone expects you to solve the problem. Here they do, but offer no [redacted] help.

I am flying East in about 10 days for a meeting in Baltimore. I shall probably remain there for 2-3 weeks since until the O^{18} expt can be done, there is little I can do here except to become impatient.

Regards to all. Please tell them that my lack of correspondence does not reflect a lack of interest. Since I shall be over in about 3½ months, gossip can wait Till then. Also nothing of interest happens in this social desert. So I would appreciate a gossip letter from Odile

Jim

Mail will reach me here if it arrives before March 11th. Otherwise write me in care of Alex Rich